Attorney Docket No.: 020154-001210US

PATENT APPLICATION

IMPLANTABLE MEDICAL DEVICES USING ZINC

Inventor(s): PAMELA CIFRA, a citizen of the Philippines residing at
6915 Skyline Boulevard
Hillsborough, California, 94010

MICHAEL D. DAKE, MD, a citizen of the United States residing at
665 Gerona
Stanford, California, 94305

CHRISTOPHER ELKINS, Ph.D., a citizen of the United States residing at
1021 Woodside Avenue
Redwood City, California, 94061

JACOB M. WAUGH, MD, a citizen of the United States residing at
4020 El Camino Real, #2204
Palo Alto, California, 94306

Assignee: Essentia Biosystems, Inc.
656 Hale Street
Palo Alto, California, 94301

Status: Small entity

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 650-326-2400

IMPLANTABLE MEDICAL DEVICES USING ZINC

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present invention relates generally to U.S. Patent Application Serial No. 60/421,336, attorney docket no. 020154-001100US, entitled "Modulation of Zinc Levels to Improve Tissue Properties," and U.S. Patent Application Serial No. 60/421,278, attorney docket no. 020154-001200US, entitled "Implantable Medical Devices Using Zinc," which are hereby fully incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] The present invention relates generally to medical devices. More specifically, the invention relates to implantable medical devices coupled with zinc to inhibit plaque formation, enhance elastin production or the like.

[0003] Blood vessel disease (vascular disease) frequently arises when masses or plaques, called "atheromas," accumulate on the inner walls of vascular lumens, resulting in a condition known as atherosclerosis. Atherosclerosis may occur in any blood vessel in the body, but is particularly common in the arteries supplying blood to the heart and the arteries supplying blood to the lower extremities. Atherosclerosis occurs naturally as a result of aging, but may also be aggravated by factors such as diet, hypertension, heredity, vascular injury and the like. Atheromas and other vascular deposits restrict blood flow and can cause a deficiency of blood in a body part--a condition known as ischemia. Ischemia, in turn, can result in tissue death, such as a myocardial infarction (heart attack) or gangrene of the lower extremities. Atheromatous deposits can have widely varying properties, some being relatively soft and others being fibrous or calcified.

[0004] One method for treating vascular disease includes placing one or more stents within a blood vessel at a site of atherosclerosis. Stents are commonly used to treat an obstructed or weakened vascular lumen by supporting the vessel wall to maintain patency of the lumen. In many procedures, a blood vessel is first dilated, using a balloon angioplasty catheter or similar device, and then one or more stents are placed across the dilated area to maintain its diameter.

[0005] Although the use of stents has greatly improved treatment of ischemic vascular disease, one shortcoming of stents which has not been resolved is the frequent occurrence of in-stent restenosis. Restenosis refers to the process of proliferation and migration of smooth

muscle cells towards an area of the blood vessel wall in and around the area of an implanted stent, causing reclosure or blockage of the blood vessel. Thus, restenosis may result in ischemic conditions, such as heart attack, which the stent or stents were intended to prevent. Many researchers are currently investigating devices and methods for preventing such restenosis, such as coating stents with drugs or treating stents with radiation. Currently available devices, however, have not fully solved the restenosis problem.

[0006] Zinc is one of the most important trace elements in human health and nutrition and plays a significant role in the function of many intracellular proteins. Zinc is crucial for gene expression and nucleic acid metabolism, which accounts in part for its importance in cellular growth and differentiation. Recent investigations indicate that zinc may actually have a regulatory role. Zinc possesses ligand-binding properties that are utilized effectively at the catalytic site of a broad range of enzymes. In addition, it has many structural roles in biological membranes [Tang et al., (2001) J. Nutr. 131: 1414-14200], cell receptors, and proteins (i.e. transcription factors and proteins involved in DNA replication). For additional description of many of the properties and characteristics of zinc, refer to U.S. Patent Application Serial No. 60/421,336, ("Modulation of Zinc Levels to Improve Tissue Properties"), previously incorporated by reference.

[0007] As is discussed further below, zinc may have one or more beneficial effects in treating vascular disease. Therefore, it would be advantageous to have implantable medical devices and methods that use zinc to improve one or more tissue properties in a tissue such as a blood vessel, heart muscle, a venous graft or the like. For example, zinc might be used with an implantable device in a configuration to prevent plaque formation, enhance elastin production, provide both plaque prevention and enhanced elastin production or the like. At least some of these objectives will be met by the present invention.

BRIEF SUMMARY OF THE INVENTION

[0008] Devices and methods of the present invention provide for implantable medical devices using zinc to enhance one or more properties of a tissue. For example, some methods include using an implantable medical device coupled with at least one zinc-containing component to resist plaque formation, enhance elastin production or both. The device, for example, may be one or more stents, grafts or stent-grafts for placement in a blood vessel such as a coronary artery, peripheral blood vessel, abdominal aorta or the like. In other embodiments, the device may comprise a gel or other zinc carrier substance, a catheter such

as a balloon-expandable catheter, a zinc anchoring substance or device, or any other suitable device. The at least one zinc-containing component, and the amounts, concentrations, methods for coupling the zinc to the device and the like may be selected to provide a desired effect on a target tissue. Generally, a "zinc-containing component" refers to a zinc compound, complex, chelate or any other zinc-containing component. Target tissues may be any suitable tissues, such as blood vessels, heart muscle, aneurismal tissue, manufactured graft material, genetically-engineered tissue, animal tissue or the like.

[0009] In one aspect, a method for resisting plaque formation in a tissue includes: providing at least one implantable medical device; identifying a configuration of at least one zinc-containing component which, when coupled to the at least one implantable device and implanted in the blood vessel, will inhibit plaque formation; coupling the at least one zinc-containing component to the implantable medical device in the identified configuration; and implanting the at least one device so that the zinc-containing component inhibits plaque formation. In some embodiments, for example, the tissue may include arterial tissue, venous tissue, heart tissue, natural graft tissue, man-made graft tissue or genetically engineered tissue. The device may be any suitable device. In some embodiments, the device is a stent, a graft, a stent-graft, a gel, a carrier, a zinc-anchoring device, a compound, a balloon-expandable device or a catheter. In one embodiment, for example, the device includes a biodegradable stent.

[0010] As described above, the at least one zinc-containing component may comprise any suitable zinc substance or combination. In some embodiments, for example, the at least one zinc-containing component comprises one or more zinc salts, such as acetate, ascorbate, aspartate, butyrate, caproate, caprylate, carbonate, chromate, citraconate, citramalate, citrate, EDTA, formate, fumarate, gallate, gluconate, halides, iodate, lactate, laurate, laureate, malate, maleate, malonate, metaphosphate, methansulfonate, monophosphate, myristate, nitrate, octoate, oleate, orotate, orthophosphate, oxalate, oxides, palmitate, permanganate, phenolsulfonate, phosphate, picolinate, propionate, pyrophosphate, salicylate, selenate, stearate, succinate, sulfate, sulfonate, tannate, tartrate, tetrametaphosphate, titanate, transferrin, tripolyphosphate, undecylate, or valerate.

[0011] Optionally, a zinc-containing component for use in the present invention may be selected to provide ionic zinc when the device is implanted in the blood vessel. Also optionally, an amount of zinc may be selected to provide an ionic zinc concentration in an

area of the blood vessel adjacent the implanted device of between about 1.0 picomolar and about 500 millimolar. In various embodiments, a concentration or amount of zinc may be selected to provide plaque inhibition for at least a target duration. For example, the target duration in one embodiment may be at least about six months. In some embodiments, the configuration a zinc-containing component provides for sustained-release of ionic zinc from the device.

[0012] Zinc-containing components may be coupled with a medical device in any suitable configuration or by any suitable means. In one embodiment, the at least one zinc-containing component is selectively deposited over a portion of the device. For example, the zinc-containing component may be deposited primarily on a tissue-facing surface of the device. In other embodiments, an entire device may be coupled with or coated in zinc.

[0013] In one embodiment, coupling the zinc-containing component to the implantable medical device includes coupling a zinc chelator to the device and releasably coupling the zinc-containing component to the chelator. Optionally, the method may further include polymerizing the chelator.

[0014] In another aspect, a method for treating a blood vessel includes: identifying a diseased location along the blood vessel for treatment; determining that the blood vessel at the diseased location is susceptible to plaque formation if treated by device implantation; selecting an implantable medical device coupled with at least one zinc-containing component in response to the determining step; and implanting the selected medical device along the diseased location such that the zinc-containing component inhibits formation of plaque. As with the method just described, any suitable device, any form of zinc, any means for coupling zinc to the device, any amounts or concentrations of zinc or the like may be selected in any given embodiment to provide desired effects on a tissue.

[0015] In another aspect, a method for coupling at least one zinc-containing component with an implantable medical device to enhance plaque resistance, elastin production or both, of a tissue includes coupling at least one binding agent with at least one surface of the implantable medical device and coupling the at least one zinc-containing component with the at least one binding agent. In some embodiments, coupling the at least one binding agent with the at least one surface involves coupling a chelator with the surface. As mentioned above, the method may further include polymerizing the chelator. The binding agent may be any suitable binding agent, but in one embodiment it includes allylamine linked with

polyaspartate, with the zinc-containing component being coupled with the polyaspartate. Again, any suitable implantable device, any suitable form or amount of zinc and any suitable means for coupling the zinc with the device may be used.

[0016] In yet another aspect, a method for enhancing elastin production of a tissue includes: identifying an area of tissue which may benefit from enhanced elastin production; implanting at least one implantable medical device at or near the area of tissue, the device comprising at least one zinc-containing component; and promoting elastin formation at or near the area of tissue with the zinc-containing component of the implantable medical device. As with the method described above, the tissue may be arterial tissue, venous tissue, heart tissue, natural graft tissue, man-made graft tissue or genetically engineered tissue in various embodiments. For example, the area of tissue may comprise an area within or adjacent to an abdominal aortic aneurysm. Here again, any device, form or amount of zinc, or means for coupling may be used.

[0017] In some embodiments, the promoting step raises elastin content of the area of tissue to an enhanced elastin content which is significantly greater than a normal elastin content. Sometimes, the area of tissue has the normal elastin content prior to the implanting step. In some embodiments, the identifying step comprises identifying an area of tissue which has a deficient elastin content which is significantly less than a normal elastin content.

[0018] In another aspect, a device for inhibiting plaque formation, promoting elastin production, or both includes at least one implantable medical device and zinc-containing component coupled with the device. In various embodiments, the device may be a graft, a stent, a stent-graft, a gel, a zinc-anchoring device, a topical compound or complex or any other suitable device. The zinc-containing component may be a zinc salt, as described above, or may be a zinc chelate or any other form of zinc.

[0019] In some embodiments, the device is configured to provide ionic zinc when the device is implanted. For example, an ionic zinc concentration may be provided in an area adjacent the implanted device of between about 1.0 picomolar and about 500 millimolar. As described above, configurations of zinc, coupling methods, amount and concentrations, and the like may be varied to achieve desired effects on a tissue. The various embodiments are described in more detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] Fig. 1 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc bound to a surface of the device via a binding agent, according to one embodiment of the present invention.

[0021] Fig. 2 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc bound to a surface of the device via a polymerized binding agent, according to one embodiment of the present invention.

[0022] Fig. 3 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc bound to a surface of the device via multiple different binding agents, according to one embodiment of the present invention.

[0023] Fig. 4 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc coupled with a surface of the device via a electroplating or sputter-coating techniques, according to one embodiment of the present invention.

[0024] Fig. 5 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc coupled with a surface of the device via a gel, according to one embodiment of the present invention.

[0025] Fig. 6 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc coupled with a surface of the device via a gel and a binding agent, according to one embodiment of the present invention.

[0026] Fig. 7 is a cross-sectional diagram depicting a portion of an implantable medical device with a surface modified with allylamine to form part of a zinc-binding agent, according to one embodiment of the present invention.

[0027] Fig. 8 is a cross-sectional diagram depicting a portion of an implantable medical device with zinc coupled with a surface of the device via a binding agent formed from allylamine, as in Fig. 7, couple with polyaspartate, according to one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0028] Devices and methods of the present invention generally include at least one implantable medical device, such as a stent or graft, coupled with at least one zinc-containing component for treating a tissue, such as a blood vessel, heart tissue, a vein graft or the like. Generally, a determination is made as to what effect on the tissue is desired and then a configuration of a zinc-containing component is chosen for coupling with an implantable

device. As mentioned above, a zinc-containing component may be a zinc compound, complex, chelate, or any other suitable form of zinc or combination of forms of zinc. Different configurations of zinc may be used, for example, to inhibit plaque formation, promote elastin production, or both, in various embodiments. One configuration of zinc coupled with a stent, for example, may be advantageous for preventing plaque formation in a coronary artery. Another configuration may work well for preventing plaque formation on a vein graft. Yet another configuration may be advantageous for promoting elastin production in or near an aneurysm. In some embodiments, both plaque inhibition and elastin promotion may be achieved.

[0029] Generally, any configuration of at least one zinc-containing component may be used with any implantable device, according to various embodiments. Devices may include any of a number of implantable devices, such as stents, grafts, stent-grafts, and the like. For the purposes of this specification, the word "device" is defined as any means for carrying or applying zinc to a tissue or other surface. For example, in some embodiments, a device may comprise a topical zinc-containing component which may be applied to a tissue to release the zinc to achieve a desired effect. In other embodiments, a device may comprise a gel, a container for releasably carrying zinc, an anchoring device for anchoring zinc to a tissue or the like. Thus, the embodiments of various devices described below, such as stents and grafts, should not be interpreted to limit the scope of the present invention or the meaning of the word "device." Any device may be used in accordance with the present invention.

[0030] Devices of the invention, therefore, may include any means for delivering or applying zinc at a desired location. The location will typically be on or near a tissue. In some embodiments, the tissue may be tissue of a human patient, such as heart muscle, arterial wall tissue, venous tissue, and the like. In other embodiments, the tissue may comprise graft tissue, such as a venous graft. In still other embodiments, zinc may be used in a research or therapeutic context on manufactured tissue, genetically engineered tissue, animal tissue or the like. Generally, application to any tissue is contemplated, such as human, animal or other tissue in research, patient care or other suitable contexts.

[0031] Similarly, any configuration of zinc may be used with the present invention. In general, devices and methods of the invention provide for delivering ionic zinc at or near a tissue for treatment. However, any suitable form of zinc may be coupled with one or more devices to deliver zinc and all forms of zinc now known or hereafter discovered are

contemplated. Additionally, any suitable concentration, amount, chemical configuration, and the like may be used. In some embodiments, for example, zinc may be applied to a tissue-contacting surface of a stent. In other embodiments, the zinc may be applied to the entire stent or some other surface of the stent. For various desired effects, a device may be coated in different thicknesses of zinc, may be coupled with zinc to provide sustained-release of the zinc, may be coupled with varying concentrations of zinc or the like. Zinc may also be coupled with a device by any suitable means. Various embodiments may also employ different means for coupling zinc with a device. For example, zinc chelators or other binders may be used to bind zinc to a surface of a device, zinc may be bound to a device by electroplating or any other suitable method may be used. Thus, any suitable medical devices and any suitable configurations, amounts, compositions, and the like may be used according to the present invention.

[0032] As just described, zinc coupled or otherwise used with one or more devices according to the present invention may have any suitable composition. As mentioned above, zinc used in the present invention is typically referred to as "at least one zinc-containing component," which may include but is not limited to at least one zinc compound, complex, chelate, a combination thereof or the like, in various embodiments. In some embodiments, for example, one or more zinc salts may be used. Suitable zinc salts include, but are not limited to acetate, ascorbate, aspartate, butyrate, caproate, caprylate, carbonate, chromate, citraconate, citramalate, citrate, EDTA, formate, fumarate, gallate, gluconate, halides, iodate, lactate, laurate, laureate, malate, maleate, malonate, metaphosphate, methansulfonate, monophosphate, myristate, nitrate, octoate, oleate, orotate, orthophosphate, oxalate, oxides, palmitate, permanganate, phenolsulfonate, phosphate, picolinate, propionate, pyrophosphate, salicylate, selenate, stearate, succinate, sulfate, sulfonate, tannate, tartrate, tetrametaphosphate, titanate, transferrin, tripolyphosphate, undecylate, and valerate. Also usable in the invention are chelates of zinc and other types of zinc-containing chemical substances such as complexes, for instance complexes of zinc with amino acids such as methionine.

[0033] In some embodiments, a zinc-containing component may be selected or coupled with a device in a manner to provide controlled-release or sustained-release of zinc at a desired location. For example, a zinc-containing component may be coupled with a device with varying degrees of "releasability," such that some zinc will be released soon after

implantation and other zinc will be released over time. In other embodiments, zinc may be coupled with or contained within, a degradable device such as a degradable stent, capsule, other anchoring device or the like, so that as the device degrades over time, zinc is released in a sustained or controlled manner. In further exemplary embodiments, a zinc-containing component may be contained within matrixes, liposomes, vesicles, microcapsules, microspheres, a solid particulate material or the like, to provide release of zinc over time.

[0034] Generally, any suitable time period for release of zinc may be chosen, depending on the desired effect, the tissue being treated, the desired duration of treatment, and the like. In some embodiments, for example, it may be desired to cause a release of zinc very soon after implanting a device, to reach a plateau level of zinc release relatively quickly, and to sustain that level of release over a longer time period. In one embodiment, for example, a desired level of zinc at a treatment location may be reached within two weeks of implanting a device and that level may be maintained for at least six months. Any other sustained-release or controlled-release pattern is contemplated with the scope of the invention.

[0035] The amount, concentration, composition or any other characteristic of zinc used with devices of the present invention may be selected to provide one particular effect or a combination of effects on a target tissue. In some embodiments, for example, zinc coupled with a device will be configured to inhibit plaque formation in a treatment area, such as within a coronary artery. In another embodiment, zinc may be coupled with a device to enhance elastin production, for example, to enhance elastin production at or near an aneurysm. In some embodiments, zinc coupled with a device may cause both plaque inhibition and enhanced elastin production. Any one or a number of variables applying to devices, zinc-containing components or both may be selected to achieve desired effects on a given tissue, while still remaining within the scope of the present invention.

[0036] As mentioned above, embodiments of the present invention generally include at least one implantable medical device (as device is defined herein) coupled with at least one zinc-containing component. Devices, zinc-containing components, and means for coupling devices and zinc are typically selected to provide for the release of ionic zinc from the device at a location to have a desired effect on a tissue or similar substance. For example, devices used in various embodiments of the present invention may be made by various known techniques, such as those described in U.S. Patent Nos. 6,113,636, 6,190,407, 6,267,782 and 6,322,588, the complete contents of which are hereby incorporated by reference. Such

techniques involve depositing a metal or compound, such as zinc or a zinc compound on the surface of a device (for instance a stent or implant) formed from a suitable biocompatible material such as stainless steel, titanium, nitinol, ceramics, polytetrafluoroethylene, silastic, polylactide, polyglycolide, polylactide-co-glycolide, and the like, acrylates, methacrylates, polyurethane, or combinations of these. Other biocompatible materials or compounds may similarly be used in such devices. Deposition may be carried out either on a device already formed or on biocompatible material that will subsequently be used for production of such a device. The deposition is carried out by techniques such as incubation of the device or biocompatible material with a solution of a zinc salt, as described in US Patent No. 6,113,636. Alternatively, the zinc may be deposited on the device or biocompatible material in the form of elemental zinc. U.S. Patent No. 6,113,636 describes processes for producing such a zinc-containing material, including chemical reduction, photochemical reduction, and electrodeposition or electroplating. Also, as described in that patent, a combination of elemental zinc and a zinc salt may be deposited on the material.

[0037] U.S. Patent No. 6,267,782 describes additional means for producing a zinc- or zinc salt-containing biocompatible material or device, including physically impressing the elemental zinc onto the material or device, mixing elemental zinc into the substance used to form the biocompatible material, such as a polymer during its formation, and vapor deposition. U.S. Patent No. 6,322,588 contains additional information about deposition of metals on such biocompatible materials.

[0038] As discussed above, the amount of a zinc-containing component that is coupled with a device may generally be selected to provide an effective amount of zinc ions to achieve a desired effect for a desired time period. For example, embodiments of the invention typically include one or more implantable medical devices used to increase tissue zinc levels in order to prevent plaque formation or to increase tissue elasticity or elastin levels. Such devices include, for example, vascular devices such as stents, grafts, stent-grafts, catheters, gels, topical compounds, zinc anchoring devices, and the like, which may be implanted to reverse elastin degradation states, treat atherosclerotic vascular diseases, repair or prevent aneurysmal disease or the like. In one embodiment, for example, intravascular stents are coated with one or more zinc-containing components to prevent or treat plaque progression or restenosis.

[0039] In some embodiments, zinc is coupled with a device so as to provide a desired concentration of zinc ions at a given location on or in a tissue. For example, in one

embodiment, at least one zinc-containing component is coupled with a device so that a zinc concentration at or adjacent to a target tissue, upon implantation of the device, will be from about 1.0 picomolar to about 500 millimolar, and more preferably from about 100 picomolar to about 50 millimolar. These concentration ranges are approximated at the tissue-device interface, but may also occur in an area around or adjacent to that interface. The ranges listed above may have plaque inhibition effects, elastin promotion effects, or both, in various settings. Other ranges may be selected to provide other or additional effects on a target tissue.

[0040] Although devices such as stents, grafts, stent-grafts and the like have been occasionally emphasized as exemplary embodiments, it should be emphasized again that any suitable means for delivering or applying zinc to a tissue is contemplated. For example, in one embodiment, zinc is applied directly to a venous bypass graft for implantation to bypass a coronary artery. It has been found that zinc, applied once to a venous graft after implantation, may enhance elastin production in or near the graft and thereby prevent graft atherosclerosis. It may be applied as a gel, another form of topical compound, or any other suitable delivery agent coupled with zinc. Furthermore, a zinc gel or other applicable compound may be delivered via any suitable means. In one embodiment, for example, zinc may be applied in a sustained-release form via a balloon expandable catheter. Zinc-containing components used for inhibiting plaque formation in venous grafts may provide any suitable zinc concentration at the tissue-device interface, but in one embodiment provide a concentration from about 1.0 picomolar to about 500 millimolar, and more preferably from about 100 picomolar to about 50 millimolar.

[0041] In one embodiment, for example, zinc ions may be released from a gel composition with or without other active agents. For example, ionic zinc could be released from a gel composed of cross-linked 30% polyethylene glycol dimethacrylate in phosphate buffered saline including anchoring to the surface of the stent covalently. Zinc would be included in the form of zinc acetate with phosphate buffer added to the final composition. Methacrylates would be introduced to the stent surface using a silane with a methacrylate arm (United Chemical). The gel would be UV crosslinked and anchored to the reactive stent methacrylates. Alternately, polylactide-co-glycolide microspheres containing ionic zinc and preferably a pH buffer could be incorporated into the gel or otherwise anchored to the stent

(for example, following methods described in "Development of a Platform to Evaluate and Limit in-Stent Restenosis," Elkins et al., Tissue Eng., 2002 Jun;8(3):395-407).

[0042] In another embodiment, zinc may be used to increase heart elastin content and improve compliance. In one embodiment, a gel, patch or other device coupled with zinc is used to increase tissue free ionic zinc levels in order to enhance elastin production in or increase compliance of heart tissue. This application may be of particular interest following heart attack or to minimize symptoms from heart failure. In one embodiment, the concentration range of the zinc-containing substance is from about 1.0 picomolar to about 1000 millimolar, and preferably from about 100 picomolar to about 900 millimolar. As in the stent and vascular graft examples above, zinc could be applied via a gel (with or without another device), a patch applied outside the heart or any other device applied to the heart. The zinc can be metal (applied by sputtering, plating, or other means), chelate (including poly-binding agents as above) or salt. The zinc-containing component can be mechanically or chemically adhered so that ionic zinc is made available to the tissue over time.

[0043] One exemplary method might proceed as follows. After myocardial infarct, endoscopic delivery of a sterile 20% pluronic f-127 (BASF) gel containing buffered bioerodable PLGA microspheres loaded with zinc acetate could be accomplished with injection into the myocardium just deep to the pericardium. In this manner, zinc ions could be released during infarct remodeling so that the scarred tissue would be elastic and provide an inward force to assist the remaining myocardium in ejecting blood. In this manner, symptoms of heart failure might be reduced. The same approach could be accomplished through a variety of techniques including intracardiac delivery through endovascular access. These approaches could be combined with laser or other techniques and therapeutic agents as well.

[0044] Referring now to Figure 1, a portion of a stent 10, having a surface 11, is shown in cross section, with a plurality of zinc ions 14 attached to surface 11 via a plurality of binding agents 12. Generally, stent 10 may be a stent, graft or any other suitable implantable device useable with zinc. Zinc ions 14 may comprise any of the zinc-containing components described above, or any combination of zinc-containing components. Similarly, binding agents 12 may include any suitable binding elements for coupled zinc ions with one or more surfaces 11 of stent 10. In some embodiments, binding agents 12 comprise one or more zinc chelators.

[0045] Figure 2 shows a similar cross section to that in Figure 1, except that zinc ions 14 are bound to surface 11 via chains of binding agents 12. Such chains of binding agents 12 allow larger numbers of zinc ions 14 to be bound to stent 10 per unit surface area of surface 11. Therefore, higher doses of zinc may be administered via the same stent 10 as in Figure 1.

[0046] Figure 3 demonstrates that multiple different binding agents 12a-c may be used to bind zinc ions 14 to one or more surfaces 11 of the same stent 10. Use of multiple binding agents 12a-c may allow stent 10 to release zinc ions 14 at different rates, to provide for timed- or sustained-release of zinc at a treatment area.

[0047] Figure 4 shows a similar stent 10 in cross section, however zinc ions 14 have been electroplated or sputter-coated onto surface 11. The portion of stent 10 to the right of the vertical dotted line shows that when a stent plated or sputter-coated with zinc 14 is placed in an in-vivo environment, in which there is oxidative stress, zinc ions 14 are released from stent 10.

[0048] Figure 5 illustrates a cross section of stent 10 having a gel coating 13 which includes zinc ions 14. As in the previous examples, zinc ions 14 will be released in vivo over time, either as a result of oxidative processes, due to gel degradation or both. In still other embodiments, as shown in Figure 6, zinc may be bound to surface 11 of stent 10 by a combination of gel coating 13 and one or more binding agents 12. Such combinations may achieve advantageous zinc release patterns or timing to enhance treatment.

[0049] Figure 7 shows one possible embodiment of a binding agent for zinc ions 14. In Figure 7, allylamine 15 may first be bound to surface 11 to generate a reactive primary amine which may then be coupled with a single aspartate 17 via an amide linkage. Aspartate 17 then serves as a binding agent to bind zinc 14. Figure 8 shows surface 11 modified with allylamine 15 to generate a reactive primary amine which is then coupled to polyaspartate 16 via an amide linkage. Each aspartate can then serve as a zinc binding agent. As designated by the subscript letters "n" and "m", the number of zinc ions does not necessarily equal the number of aspartates.

[0050] The following examples are provided by way of illustration only and not by way of limitation.

[0051] Example 1. Zinc anchored to a stent through chemical binders or chelates for controlled release after stent deployment

[0052] For the purposes of this example, a commercially available Cordis BX-Velocity™ stent (Cordis, Miami, FL) was used as a starting device, though any suitable stent device could be used. Stents were pretreated in a plasma chamber at 400 watts for 3 minutes in an Argon atmosphere, then derivatized in plasma for 4 minutes with a 18 milliliters/hour allylamine flow in an Argon atmosphere at 400 watts, followed by an argon flush for 3 minutes. This treatment generated reactive amine sites on the surface of the stent, as depicted schematically in Figure 7. Other functionalities could be introduced chemically, physically or through plasma for the same purpose. The degree of functional derivatization may be evaluated with surface scanning IR, using multiple bounce attenuated total reflectance for example, or through binding a color compound or fluorescent compound to the surface.

[0053] A suitable linker was then used to anchor a zinc binding agent to the reactive amines on the stent surface, as shown schematically in Figures 7-8. As a variation of this strategy, a chain of linkers could be used to bind multiple zinc atoms per chain to remove constraints of surface area and increase total zinc dose. These chelators release zinc ions over time, with time course dependant primarily upon the identity of the chelating agent. Secondary impact of local pH and oxidative stress after injury can be used to add a "smart" environment sensitive component to zinc release.

[0054] Among zinc compounds, particularly useful in the compositions and methods of this invention are zinc salts, including acetate, ascorbate, aspartate, butyrate, caproate, caprylate, carbonate, chromate, citraconate, citramalate, citrate, EDTA, formate, fumarate, gallate, gluconate, halides, iodate, lactate, laurate, laureate, malate, maleate, malonate, metaphosphate, methansulfonate, monophosphate, myristate, nitrate, octoate, oleate, orotate, orthophosphate, oxalate, oxides, palmitate, permanganate, phenolsulfonate, phosphate, picolinate, propionate, pyrophosphate, salicylate, selenate, stearate, succinate, sulfate, sulfonate, tannate, tartrate, tetrametaphosphate, titanate, transferrin, tripolyphosphate, undecylate, and valerate. Also usable in the invention are chelates of zinc and other types of zinc-containing chemical substances such as complexes, such as complexes of zinc with amino acids such as methionine. Typically, zinc binding agents with fewer than 6 carbon atoms per zinc atom provide rapid release of zinc. Combinations of different binding agents (some short and some long) as well as chains of binding agents can accomplish longer term delivery of zinc atoms with complex release curves as desired.

[0055] In this example, particularly useful as linkers are any carboxylate-containing compounds, which can be used to form an amide linkage to the stent free amine groups. For example, in one embodiment the stent was immersed in polyaspartate (Ajinomoto, Japan) after appropriate pretreatment with EDC and NHS. To 5 milliliters activation buffer (0.1M MES, 0.5M NaCl, pH=6.0), 50 microliters sodium polyaspartate solution (n-asp) (30% v/v) was added. About 6 milligrams EDC and 4 milligrams NHS were then added and dissolved in the n-asp solution. The solution was allowed to react for 15 minutes at room temperature. Then, the aminated stent was fully immersed in the activated n-asp solution for 2 hours. The stent was removed, rinsed in deionized water and allowed to dry thoroughly. The carboxylate of aspartate is known to serve as a zinc chelator in other applications (for example US Patent No. 5,059,416), so such an anchored polyaspartate chain represents an anchored binding agent for multiple zinc ions which can be released over time (Figure 12).

[0056] Example 2. Local application of a zinc formulation to create a plaque-resistant artery after arterial stent deployment

[0057] The stent design is based on the Palmaz-Schatz coronary stent. Stents were either electroplated with zinc or left untreated. Electroplating was accomplished via immersion of the stent as the cathode in a 1.5 molar zinc acetate solution and running at fixed current mode at 270 milliamps (controls at 300 watts and 300 volts, but current limiting) for 5 minutes. Plated stents were rinsed in deionized water 5 times, inspected on a metallurgical microscope, mounted on balloons, and lyophilized overnight. Sputtering of zinc or deposition of zinc-containing compound would accomplish the same end in a more controlled fashion. Additionally, polishing of the surface would be desirable to allow less irritation on implantation in vivo. However, polishing often requires a thicker deposition of zinc to offset losses during polishing. It is often desirable to minimize pH reducing effects in vivo, through either avoidance of acid or through buffering or neutralizing acid during these processes. Methods of plating implantable stents are well known in the art, for example, as described in U.S. Patent Application Serial Nos. 366022 and 803843 and U.S. Patent No. 6,099,561.

[0058] Age-matched adult male New Zealand White rabbits weighing 3.8-4.2 kilograms were used in accordance with NIH and institutional guidelines (n = 3 animals per group). Under general anesthesia, an arteriotomy at the femoral artery was performed and a 5 Fr introducing sheath was placed. Under fluoroscopic guidance, stents were deployed in the infra-renal abdominal aorta. Stents were post-dilated at 8 atmospheres with a 5 millimeter

angioplasty balloon (Jupiter, Cordis, Miami, FL) to a final lumen size of 125% above the baseline with care taken to ensure that no branches were present within the stent segment. Pre- and post-deployment digital subtraction angiograms were recorded for the blank procedural control and angiostatin treatment groups. The rabbits were fed a 0.25% cholesterol diet after the intervention.

[0059] After 28 days, animals underwent total-body perfusion-fixation with immediate excision of the aortic segment containing the stent. The specimens were fixed in 10% neutral buffered formalin and were embedded in PolyBed™ (Polysciences, Warrington, PA) for light microscopy and morphologic analysis. For 28-day specimen analysis (n = 3 animals per group), each plastic-embedded aorta was cut into five pieces longitudinally equal lengths. These pieces were gross-stained by modified Verhoeff Von Giesson elastic staining. One cross sectional image of the stained aorta was obtained per zone (n = 15 sections per group). High resolution digital images of histological cross sections were acquired at 100X magnification from a Diagnostic Instruments SPOT true-color camera (Diagnostic Instruments, Sterling Heights, MI) as displayed on a Nikon E600 with Plan Apochromat™ Lenses. Using Image Pro Plus™ software (Media Cybernetics, Silver Spring, MD), the cross-sectional area of the intima and the media were determined by a blinded observer. The ratio of intima area to media area was subsequently tabulated for each. Mean, standard error, and significance were determined. Results are presented as Table 5 below.

[0060] Table 1. Ratio of intima to media area as measure of in-stent plaque progression 28 days after implantation of polished unplated control stents or unpolished Zn plated stents. (P=0.0001)

	Mean	Standard Error
Control	1.98	0.08
Zn-plated	1.42	0.07

[0061] Overall, local availability of ionic Zn from electroplated stents is afforded by local oxidative stress post stenting or post injury. These levels afford significant increases in elastin content and significant reductions in plaque progression. Increased elastin content may further stabilize what plaque does form. Incidentally, one of the factors in limiting plaque progression is surface smoothness. Here, the control is electropolished, while the Zn-

plated stent is rough and unpolished. In spite of what should be a strong pro-plaque effect, the Zn-plated stent demonstrates significant plaque reduction and stabilization.

[0062] Example 3. Local application of a zinc formulation to enhance elastin in an artery

[0063] This example is especially relevant to aneurysm management or prevention. In this example, a gel is applied directly to the artery. However, the same method can be accomplished by gel-based release from a stent-graft or a vascular graft. Such a strategy could anchor gel or even a direct zinc binding agent as in the stent examples above directly to the graft surface, the stent surface or both where appropriate. Zinc could be covalently bound or mechanically adhered as desired. Here, zinc acetate is used, but any source of zinc ions including polymerized zinc binding agents (as in the stent example above) could be applied and such agents could be covalently or noncovalently attached to the gel components themselves or the graft/stent surfaces.

[0064] In the present example, Male New Zealand White rabbits (3.0-3.5 kilograms) were used in accordance with NIH and institutional guidelines (n=3 animals per treatment group). Under general anesthesia (ketamine/xylazine induction and halothane maintenance), the right common femoral artery was isolated and adventitia circumferentially exposed. A 2 millimeter x 2 centimeter SAVVY angioplasty balloon (Cordis, Miami, FL) was introduced via arteriotomy in the superficial femoral artery and advanced into the common femoral artery. The balloon was inflated to 6 atmospheres in two 1-minute cycles then withdrawn. To ensure circumferential distribution around the common femoral artery, 20% polyethylene glycol dimethacrylate (MW 1000, Polysciences, Warrington, PA) was applied perivascularly for either gel alone or gel with 100 millimolar Zn acetate (pH 7.2) at n=3 each. After closure, the animal was initiated on 0.25% cholesterol diet.

[0065] At 28 days after mechanical dilation and perivascular delivery of gel, treated arteries (n=3 per group at 28 days) were perfusion-fixed and harvested. Harvested arteries (approximately 1.5 centimeter in length) were post-fixed in 10% neutral buffered formalin and divided into three equal segments prior to paraffin embedding. Serial (5 millimeter) cross-sections were obtained from the proximal face of each segment. Verhoeff von Giesson-Masson trichrome double stain was performed on two sections per arterial segment. Representative digital microscopic images depicted increased elastin content obtained from a Diagnostic Instruments SPOT true-color camera as displayed on a Nikon E600

epifluorescence microscope with plan apochromat lenses. Zinc was shown to cause dramatic increases in arterial elastin content.

[0066] Example 4. Local application of a zinc formulation to create a plaque-resistant or stenosis-resistant venous segment

[0067] This example is especially relevant to coronary bypass grafting, particularly with vein grafts. Additionally, this example is relevant to preventing stenosis of veins during or after venous access or in arterio-venous fistulae. All animal experiments were performed in accordance with NIH and institutional guidelines. New Zealand White male rabbits (n=3 per treatment) weighing 2.5 to 3.5 kilograms underwent general anesthesia with isofluorane (3%) after induction with ketamine (22 milligrams/kilograms) and medethomidine (225 μg/kilograms). Prior to the incision, an antibiotic prophylaxy was given with cefazolin (15 milligrams/kilograms) intravenously. A 3 centimeter segment of left superficial femoral vein was dissected through a transversal incision in the groin. All side branches were ligated with 10-0 nylon suture (Ethilon 2820G, Ethicon Inc., NJ) and divided. The animal was heparinized (200 UI/kilograms) and the vein clamped proximally and distally. The vein was catheterized with a 27 gauge needle. Three centimeter of the right superficial femoral artery was dissected through a transversal incision in the groin. At the end of the incubation period the vein was harvested and rinsed with normal saline. The right Superficial Femoral Artery was clamped just below the deep femoral artery and tied 1.5 centimeter below the proximal clamp with a 6-0 polypropylene suture (Prolene, Ethicon Inc., NJ). Under surgical magnification, a proximal longitudinal arteriotomy was performed between the clamp and the stitch and the vein anastomosed in a reversed end-to-side fashion using interrupted 10-0 nylon suture (Ethilon 2820G, Ethicon Inc., NJ). The SFA was then clamped distally and the distal anastomosis was performed 1.5 centimeter below the proximal anastomosis using the same technique. A 20% polyethylene glycol dimethacrylate (MW 1000, Polysciences, Warrington, PA) gel was applied perivascularly - either gel alone or gel with 10 millimolar Zn acetate (pH 7.2) at n=3 each. The clamps were removed, lidocaine 0.5% was applied locally to reduce spasm and the wounds were closed in two layers. After surgery, animals were maintained on a diet containing 0.25% cholesterol until vein graft harvest at 28 days. Similar effects could be obtained by using any of the stent- or graft-based devices for anti-plaque or pro-elastin deposition in veins. These approaches, particularly stent-based release

of ionic zinc according to the methods described herein are also particularly relevant to venous access stenoses and venous coronary bypass grafts.

[0068] Twenty-eight days after surgery and delivery of gel alone or Zn gel (n=3 per group for 28 day time points), animals underwent total-body perfusion-fixation as previously described [Patti et al. (1988) J Clin Invest 101:1519]. The graft was post-fixed in 10% neutral buffered formalin for 14-18 hours and divided into three segments corresponding to proximal anastomosis, mid graft portion, and distal anastomosis. Serial cross-sections (4 millimeters) were obtained from the proximal face of each segment using a standard microtome. Three random cross sections per vessel (one per segment) were obtained by a blinded observer for each processing method detailed below. Routine methods were employed for the Verhoeff von Gieson-Masson trichrome double staining. A Diagnostic Instruments SPOT (Diagnostic Instruments, Sterling Heights, MI) true-color digital camera was used to record noninterpolated microscopic images of each slide at high resolution as displayed on a Nikon E600 epifluorescence microscope with plan apochromat lenses. The resulting images were analyzed using the Image-pro Plus analysis system (Media Cybernetics, Silver Spring, MD) to determine the intima to media ratio of each based upon area measurements. The mean and standard error for all analyses were determined for each group with statistical comparisons made using one factor ANOVA repeated measures with significance evaluated at 95% and with Bonferroni, Tukey-A, and Student-Newman-Keuls post-hoc testing performed in Statview or SPSS 6.1 for the Macintosh (Prentice Hall, Upper Saddle River, NJ), and individual p-values determined as reported in text. Overall, veins treated with Zn reveal increased elastic performance and dramatic decreases in plaque formation.

[0069] Although the foregoing completely and accurately describes many embodiments of the present invention, change, additions and alterations to the described embodiments may be made without departing from the scope of the invention as defined by the following claims.